REMARKS

Reconsideration of the above-identified application in view of the amendment above and the remarks below is respectfully requested.

No claims have been canceled or added in this paper. Claims 1-31 have been amended in this paper. Therefore, claims 1-31 and 35-42 are pending. Of these claims, claims 35-42 have been withdrawn by the Patent Office "as being drawn to non-elected Groups." Therefore, claims 1-31 are under active consideration.

In the outstanding Office Action, the Patent Office states that "[t]he title is not descriptive" and that "[a] new title is required that is clearly indicative of the invention to which the claims are directed." In particular, the Patent Office states that "[t]he present title is directed to methods, systems, and computer program products for determining the biological effect and/or activity of drugs, chemical substances and/or pharmaceutical compositions based on their effect on the methylation status of the DNA, whereas in contrast the elected claims are specifically directed to a method for determining the biological effect and/or activity of at least one drug, chemical substance, and/or pharmaceutical composition."

In response to the above, Applicants have amended the title along the lines suggested by the Patent Office.

The disclosure stands objected to because "[p]ages 1-18 contain single spacing within paragraphs which is improper format. The specification should be presented in double spaced format. A substitute specification is requested with the appropriate corrections."

In response to the above, Applicants are submitting herewith a substitute specification (not including appendix) that is presented in double-spaced format. Accordingly, the objection to the disclosure has been overcome and should be withdrawn.

Claims 1-31 stand rejected under 35 U.S.C. 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention." In support of the rejection, the Patent Office states the following:

> Claim 1, line 5, recites the phrase "which was exposed to" which is vague and indefinite. It is unclear if the biological sample, the individual, or both were exposed to the said at least one drug. Clarification of the metes and bounds of the claim via clearer claim wording is requested. Claims 2-31 are also rejected due to their direct or indirect dependency from claim 1.
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> Claim 1, penultimate line, recites the phrase "concluding [...] on the biological effect and/or activity" which is vague and indefinite. It is clear that the conclusion is for the drug but it is unclear to what this effect and/or activity is directed. For example, the effect and/or activity can be directed to one of the individuals from step (a), it could be directed to cancer patients, or various other scenarios. Clarification of the metes and bounds of the claim via clearer claim wording is requested. Claims 2-31 are also rejected due to their direct or indirect dependency from claim 1.
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> Claims 1 (penultimate line) and 6 (line 3) recite the phrase "said at least one drug, chemical substance or pharmaceutical composition" which lacks clear antecedent basis as prior mention of these entities (claim 1, line 2) was made under an "and/or" scenario. Correction of this issue via clearer claim wording is requested. Claims 2-5 and 7-31 are also rejected due to their direct or indirect dependency from claim 1.
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> Claims 2-31 recite the phrase "according to" which is vague and indefinite. It is unclear what parameters and to what degree these parameters must be met to be considered "according to". Clarification of the metes and bounds of these claims via clearer claim wording is required.

Claims 2 (line 1), 3 (line 2), and 24 (line 2) recite the phrase "the biological sample" which lacks clear antecedent basis. It is unclear if the biological sample is referring to biological sample A or B or both from claim 1. Clarification of the metes and bounds of the claims via clearer claim wording is required.

Claims 4 (line 2) and 8 (line 2) recite the phrase "said biological sample" which lacks clear antecedent basis. It is unclear if said biological sample is referring to biological sample A or B or both from claim 1. Clarification of the metes and bounds of the claims via clearer claim wording is required.

Claim 5, lines 2-3, recites the phrase "identical individual, tissue, cell or other biological material". It is unclear if the "identical" characteristic only applies to the individual or also to the tissue, cell, or other biological material. Clarification of the metes and bounds of the claim via clearer claim wording is required. Claim 6 is also rejected due to its dependency from claim 5.

Claims 8 (line 4), 10 (line 2), and 13 (line 3) recite the phrase "the DNA" which lacks clear antecedent basis. It is unclear if the DNA is from sample A or B or both. Clarification of the metes and bounds of the claims via clearer claim wording is required.

Claims 14 (line 3) and 15 (line 3) recite the phrase "related with" which is vague and indefinite. It is unclear what parameters and to what degree these parameters must be met to be considered "related with". Clarification of the metes and bounds of the claims via clearer claim wording is required.

Claims 17 (line 2) and 25 (line 2) recite the phrase "is based on" which is vague and indefinite. It is unclear what parameters and to what degree these parameters must be met to be considered "is based on". Clarification of the metes and bounds of the claims via clearer claim wording is required.

Claim 18 (line 2) and l9 (line 2) recite the phrase "performed in such a way as" which is vague and indefinite. It is unclear what parameters and to what degree these parameters must be met to be considered "performed in such a way as". Clarification of the metes and bounds of the claims via clearer claim wording is required.

> Claim 19 (line 3), 20 (line 3), and 31 (line 3) recite the phrases "in particular", "such as", and "for example", respectively, which are indefinite claim language. These phrases render the claim indefinite because it is unclear whether the limitations following the phrases are part of the claimed invention. See MPEP §2173.05(d). Clarification of this issue via clearer claim wording is required.
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> Claim 28 (line 2) recites the phrase "the identical biological sample" which lacks clear antecedent basis. No prior mention in claim 1 was made of identical material. Correction of this issue via clearer claim wording is requested.

Applicants respectfully traverse the subject rejection. The claims have been extensively revised to address the various grounds given above. It is respectfully submitted that the claims are now definite.

Therefore, for at least the above reasons, the subject rejection should be withdrawn.

Claims 1-11, 13-21, 23-26, 28 and 31 stand rejected under 35 U.S.C. 102(e)(2) "as being anticipated by Laird et al. (P/N 6,331,393 B1)." In support of the rejection, the Patent Office states the following:

> Laird et al. disclose a method for determining methylation patterns (biological effect or activity) in genomic DNA (containing genes) after being treated with sodium bisulfite (sample A)(chemical substance)(abstract), as stated in instant claims 1, 9, and 13. Laird et al. disclose methylation amounts in a sample are quantitatively determined based on reference to a control reaction (sample B)(col. 5, lines 61-64) which represents an unexposed sample and analyzing methylation levels in samples A and B, as stated in instant claim 1. Laird et al. disclose using probes and primers to distinguish between methylated and unmethylated nucleic acid, amplifying the DNA, and detecting methylated DNA via fluorescence-based quantitative PCR (col. 5, lines 16-64) which represents selecting sites differentially methylated. Figures 7 and 8 display data that represent a knowledge base generated based on the conclusive effect of sodium bisulfite treatment, as stated in instant claim 1. The gene names (i.e. ESR1 or MyoD1) in Figures 7 and 8 represent additional information used for the conclusion data found in these figures (i.e. correlation between

MLH1 gene expression, MSI status, and promoter methylation status of MLH1 in Figure 8, col. 24, lines 30-31), as stated in instant claim 24. The x-axes in the 2-graphs of represent at least two individual rows of analyses, as stated in instant claims 17 and 25. This data presentation also shows all or a part of the sites used for the conclusion, as stated in instant claim 23. Further conclusions are drawn by Laird et al. (col. 24, lines 48-67). Laird et al. disclose in higher order eukaryotic organisms, DNA is methylated only at cytosines located 5' to guanosine in the CpG dinucleotide (col. 1, lines 14-17) which represent cytosine methylation. Laird et al. disclose contacting a DNA sample from a patient with a modifying agent, bisulfite (col. 5, lines 19-20 and 31). Laird et al. disclose various methods to identify altered methylation sites in cancer cells (col. 3, lines 3-5) and determining DNA methylation patterns at specific loci (col. 4, lines 12-15) which represents only one set of selected sites, as stated in instant claim 18. Laird et al. disclose selecting genes (col. 19, line 5) which represents a knowledge base of different classes, as stated in instant claim 19. Laird et al. disclose using PCR, sequencing, fluorescent labeling (col. 7, lines 26-65), as stated in instant claim 9. Laird et al. disclose using human colorectal adenocarcinoma (cancer) and normal nucosa (healthy) tissue samples (Figures 7 and 8; col. 22, lines 46-49), as stated in instant claims 4 and 5. Laird et al. disclose 25 match-paired normal and tumor samples with MLH1 expression level and MLH promoter methylation as well as MYOD1 control gene (Figure 8 and col. 8, line 64 to col. 9, line 12) which represent at least two methylation sites selected and analyzed in parallel, as stated in instant claims 11 and 21. Laird et al. disclose using parallel reactions with methylated, unmethylated, and control oligos of bisulfite-treated DNA samples (col. 18, lines 36-39). Laird et al. disclose analyzing methylation status of the ESR1 locus in DNA samples which is a gene that contains hypermethylatable CpG islands that undergo de novo methylation in human colorectal tissue in all normal and tumor samples (col. 18, line 67 to col. 19, line 17 and col. 22, lines 29-30) which represents methylation sites are located in methylation relevant genes related with cancer, as stated in instant claim 14. Laird et al. disclose using PCR primers and probes used for sequences representing fully methylated and fully unmethylated DNA in several genes, including ESR1 (col. 19, lines 32-40), which represents analyzing all potential methylation sties of the DNA, as stated in instant claim 10. Laird et al. disclose isolating DNA via proteinase K digestion from sperm and HCT116 (human colorectal cell line), treated with sodium bisulfite, and then the DNA samples are analyzed

> by COBRA analysis or amplification process using fluorescence-based real-time quantitative PCR (col. 16, line 55 to col. 17, line 17), as stated in instant claims 6-8. Altered DNA methylation pattern of cytosine residues is mutagenic (col. 2, lines 34-36) demonstrates the colorectal samples mentioned above represent genes related with ulcerative colitis which is a type of colon disease, as stated in instant claim 15. In Example 4, Laird et al. disclose analyzing the methylation DNA samples from the same patient (col. 22, lines 29-32) which represents analyzing methylation sites that are personalized, as stated in instant claims 16 and 28. In Example 5, Laird et al. disclose using 25 patients with tumor and normal tissue samples surgically removed (dissected tissue immediately frozen)(col. 23, lines 28-37) which represents histologically, dissected biological material from healthy and diseased individuals in instant claims 2-4. Laird et al. disclose the use of paraffin embedded samples (col. 9, lines 42-46). Laird et al. disclose using the TaqMan, Lightcycler, Sunrise technologies, as well as ABI Prism 7700 Sequence Detection System (col. 14, lines 5-20) which represent selection at least partially performed automatically by an automate or computer device and conclusions performed by a computer system, as stated in instant claims 20, 26, and 31.
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> Thus, Laird et al. anticipate the limitations in claims 1-11, 13-21, 23-26, 28, and 31.

Applicants respectfully traverse the subject rejection. Claim 1, from which claims 2-11, 13-21, 23-26, 28 and 31 depend, recites "[a] method for determining the biological effect and/or activity of at least one drug, chemical substance and/or pharmaceutical composition, comprising the steps of:

(a) obtaining a biological sample A containing DNA from at least one individual, tissue, cell or other biological material containing DNA, wherein said individual, tissue, cell or other biological material containing DNA was exposed to said at least one drug, chemical substance and/or pharmaceutical composition;

(b) obtaining a biological sample B containing DNA from at least one individual, tissue,

cell or other biological material containing DNA, wherein said individual, tissue, cell or other biological material containing DNA was not exposed to said at least one drug, chemical substance and/or pharmaceutical composition;

(c) analyzing the level of cytosine methylation at chosen sites of the DNA contained in the samples A and B;

(d) selecting the sites which are differentially methylated between the DNA in samples A and B, whereby a knowledge base is generated; and

(e) concluding from the said knowledge base on the biological effect and/or activity of said at least one drug, chemical substance and/or pharmaceutical composition of said biological sample A from step (a)."

Claim 1 is neither anticipated by nor rendered obvious over Laird et al. for at least the reason that Laird et al. does not teach or suggest a method for determining the biological effect and/or activity of at least one drug, chemical substance and/or pharmaceutical composition wherein said method comprises, among other things, obtaining a biological sample A that **was exposed** to at least one drug, chemical substance and/or pharmaceutical composition, obtaining a biological sample B that **was not exposed** to said at least one drug, chemical substance and/or pharmaceutical composition and then analyzing the level of cytosine methylation at chosen sites of the DNA contained in the samples A and B.

The Patent Office is apparently contending that the sodium bisulfite of Laird et al. constitutes the claimed drug, chemical substance and/or pharmaceutical composition. However, Applicants respectfully submit that it does not make sense to read claim 1 so that sodium bisulfite constitutes the claimed drug, chemical substance and/or pharmaceutical composition.

This is, in part, because claim 1 requires, among other things, that biological sample A **be exposed** to the claimed drug, that biological sample B **not be exposed** to the claimed drug and that the level of cytosine methylation in samples A and B then be analyzed. However, Laird et al. does not disclose exposing Sample A to sodium bisulfite and not exposing Sample B to sodium bisulfite and then analyzing cytosine methylation **after** exposure or non-exposure to sodium bisulfite. Instead, Laird et al. simply discloses using sodium bisulfite treatment **as a part of** the cytosine methylation analysis step.

As noted in the present specification, one of the principal purposes of the present invention is to provide a method for determining the effect of a drug, chemical substance and/or pharmaceutical composition on the methylation pattern of DNA. However, Laird et al. clearly teaches that sodium bisulfite treatment has **no such effect** as it does not alter the methylation state of DNA, but rather, merely acts as a tool to enable one to differentiate methylated cytosines from unmethylated cytosines.

In any event, Laird et al. does not disclose the cytosine methylation analysis of a sample that was not exposed to sodium bisulfite treatment. Consequently, not only is step (b) of claim 1 not taught or suggested by Laird et al., but so are the subsequent steps of claim 1 that refer to a sample B that was not exposed to the drug.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

Applicants note that claims 12, 22, 27 and 29-30 have not been rejected on the basis of any prior art, but rather, have been rejected solely on the basis of 35 U.S.C. 112, second paragraph. Therefore, in view of the fact that Applicants have overcome said rejection under 35 U.S.C. 112,

second paragraph, the immediate allowance of at least claims 12, 22, 27 and 29-30 is respectfully requested.

In conclusion, it is respectfully submitted that the present application is now in condition for allowance. Prompt and favorable action is earnestly solicited.

If there are any fees due in connection with the filing of this paper that are not accounted for, the Examiner is authorized to charge the fees to our Deposit Account No. 11-1755. If a fee is required for an extension of time under 37 C.F.R. 1.136 that is not accounted for already, such an extension of time is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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Dated: June 13, 2005

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on June 13, 2005.

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Edward M. Kriegsman